EXHIBIT E

EXPERT REPORT OF JANET ARROWSMITH-LOWE, M.D.

I. QUALIFICATIONS AND EXPERTISE

I am a physician licensed to practice in the state of New Mexico. I am board certified in Internal Medicine, an elected member of the American College of Epidemiology, and an elected Fellow of the American College of Physicians. I received my undergraduate degree at Duke University in 1972 and obtained my medical degree from Tulane University School of Medicine in 1979.

I have 11 years of experience with the United States Food and Drug Administration (FDA). I was a Medical Review Officer in the Division of Blood and Blood Products in the FDA Center for Biologics Evaluation and Research at FDA and in the Division of Antiviral Drug Products in the Center for Drug Evaluation. In both of these positions, I was responsible for reviewing premarket NDAs. I served as a Staff Epidemiologist in the Office of Epidemiology and Biostatistics at the FDA. In this position, I monitored the postmarket safety and effectiveness of marketed drugs, and I served as Consultant to the Centers for Drug and Biologics Evaluation and Research on epidemiologic issues and problems. Further, I was Acting Director of the Office of Surveillance and Biometrics in the Center for Devices and Radiological Health at the FDA. I was also an Epidemic Intelligence Service Officer at the National Centers for Disease Control (CDC) and Prevention in Atlanta, Georgia. In this position, I participated in CDC and FDA epidemiologic investigations of problems of national and regional interest.

A copy of my Curriculum Vitae is attached as Exhibit A

A list of cases in which I have testified as an expert over the past four years is attached as Exhibit B.

I charge $ 400 per hour for review of medical records and $500 per hour for deposition and trial testimony.

My opinions, as set forth below, are expressed to a reasonable degree of medical and scientific certainty, and are based on my training and experiences as a medical doctor, epidemiologist, and FDA medical review officer and acting director of Office of Surveillance and Biometrics. My opinions are also based on my knowledge of the requirements applicable to pharmaceutical manufacturers under the Federal Food, Drug, and Cosmetic Act and federal regulations pursuant to the Act; my knowledge of general FDA policies, procedures, and industry practices gained through my FDA and consulting experience; and my knowledge of practices in the pharmaceutical industry involving the development of innovative medicines.

II. MATERIALS REVIEWED I have reviewed a substantial number of documents relating to Neurontin®. These documents include, but are not limited to, documents from the Neurontin® IND, NDA and sNDAs; the medical officer's reviews of the NDAs; the affidavit of Cynthia McCormick, M.D., executed on September 13, 2007; documents relating to contacts between FDA and the sponsor, internal FDA documents, as well as regulations in 21 CFR part 300, which were in effect during the time Neurontin® was under development and throughout its marketing history; as well as relevant journal articles and other scientific publications. Attached, as Exhibit C, is a list of materials I have reviewed. I have also reviewed various medical articles and textbooks and rely on my professional training and experience in assessing the materials I have reviewed. In addition, I have reviewed the expert report, deposition testimony and materials considered by Cheryl D. Blume, Ph.D. I anticipate reviewing additional materials pertinent to my opinions, as they become available.

III. FDA OVERSIGHT OF PRESCRIPTION MEDICINES

A. FDA's Regulation of Prescription Medicines

The Food and Drug Administration ("FDA") is the expert federal agency charged by Congress to regulate prescription medicines. The Federal Food, Drug and Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.* ("FDCA"), established FDA as a component of the United States Department of Health and Human Services. 21 U.S.C. § 393. The FDCA also vests regulatory and enforcement authority in the Secretary of Health and Human Services. The Secretary has delegated this authority to the Commissioner of FDA. FDA Staff Manual Guides, Vol. II, § 1410.10 (available at http://www.fda.gov/smg/1410_10.html).

FDA's authority to regulate the manufacture, labeling and distribution of human medicines is aimed at promoting and protecting the public health, and FDA has been charged by Congress with the duty to ensure that medicines are "safe and effective" for their intended uses when used in accordance with the product label. 21 U.S.C. § 393(b)(2)(B). Under the FDCA, a medicine is "misbranded" if its labeling is false or misleading, or does not provide adequate warnings. *See* 21 U.S.C. § 352.

The FDA has clearly defined its role in ensuring that medicines are safe and effective. FDA has stated, "Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of its safety and effectiveness, but rather a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling." 71 Fed. Reg. 3922, 3924 (Jan. 24, 2006) (citing 21 U.S.C. 355(d)). FDA has also clearly stated that it understands its role in ensuring that prescription medicines are safe and

effective to mean that the labeling requirements it establishes are not minimal standards:

> Another misunderstanding of the act encouraged by State law actions is that FDA labeling requirements represent a minimum standard...In fact, FDA interprets the act to establish both a 'floor' and a 'ceiling,' such that additional disclosures of risk information can expose a manufacturer to liability under the act if the additional statement is unsubstantiated or otherwise false or misleading. Given the comprehensiveness of FDA regulation of drug safety, effectiveness, and labeling under the act, additional requirements for the disclosure of risk are not necessarily more protective of patients. Instead they can erode and disrupt the careful and truthful representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug.

Id. at 3934 – 5. FDA has also stated, "FDA believes that State laws conflict with and stand as an obstacle to achievement of the full objectives and purposes of Federal law when they purport to compel a firm to include in labeling or advertising a statement that FDA has considered and found scientifically unsubstantiated." *Id.* at, 3922-29.

The FDA has over 9,000 employees located in more than 150 U.S. cities. Among its staff, FDA has several thousand scientists, including physicians, chemists, pharmacologists, epidemiologists, statisticians, microbiologists and other professionals. Many of these scientists work in CDER (Center for Drug Evaluation and Research), the drug review, approval and monitoring section of the FDA. CDER is the largest drug regulatory agency in the world.

B. FDA's Drug Review and Approval Process

1. Investigational New Drugs

Since 1962, a pharmaceutical company must first submit to FDA an Investigational New Drug application ("IND") if the company intends to conduct clinical investigations with a new drug in the U.S. 21 C.F.R. § 312.20. The central focus of an IND is "the general investigational plan and the protocols for specific human studies." 21 C.F.R. § 312.22(c). FDA's "primary objectives" in reviewing an IND are to assure safety and rights of the clinical trial subjects and "to help insure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety." 21 C.F.R. § 312.22(a). The IND application contains extensive information on the manufacture of the drug, animal studies demonstrating safety for humans, pharmacologic studies, and protocols for the first studies in humans.

As part of the IND review process, FDA will review details of the chemistry, manufacturing and controls for the new drug product, animal and other *in vivo* and in vitro investigations, data on human use from other countries, including adverse events associated with the use of the drug product, and the investigational plan for the new drug. FDA scientists review and comment on the protocols submitted with the IND for the intial human use of the drug in the United States. FDA requires that the sponsor make a commitment for Institutional Review Board oversight to assure human subjects protection. The IND application must include an Investigator's brochure, which serves as labeling for the new application.

Based on initial safety information from the first clinical studies in healthy volunteers, the drug product may be studied in more extensive clinical trials to establish effectiveness as well as safety for the intended population. The FDA can, and sometimes does, place a hold on further development at the IND stage when there are questions or concerns about the possible safety of the product for use in humans. The foremost consideration for the FDA in clinical investigations is drug safety.

2. New Drug Application

After FDA permits human testing to begin in the U.S., it monitors the results and safety data from the clinical trials, along with the manufacturer. FDA may place a clinical hold on further development if a concern arises about the safety of the human subjects at any point in the drug development process. As a practical matter, drug product sponsors usually request formal meetings with the FDA review division responsible for the premarket review of the IND or NDA for their drug product to discuss essential aspects of the drug development plan. Typically, there may be a pre-IND meeting, and End-of-Phase 2 meeting and a pre-NDA meeting between representatives of the sponsor and FDA management and review scientists. In these meetings, the sponsor proposes a development plan or protocols, receives advice from FDA scientists, and may seek agreement on specific aspects of the drug development plan.

Assuming that clinical drug development progresses to the point that the sponsor believes there is sufficient data to demonstrate safety and effectiveness of the drug for a specific indication, it can submit a new drug application ("NDA") to FDA, requesting permission to market the drug in the U.S. The NDA includes, among other things, detailed descriptions of a) pre-clinical pharmacology and toxicology studies concerning the drug and its possible side effects; b) human pharmacokinetics and bioavailability studies concerning the drug; and c) clinical studies concerning the safety and effectiveness of the drug. 21 CFR § 314.50(d)(2), (3) and (5). FDA reviews the scientific and clinical research submitted in the NDA to determine whether the drug meets the "statutory standards for safety and effectiveness...and labeling." 21 CFR § 314.105(c). FDA "is required to exercise its scientific judgment to determine the kind

and quality of data and information an applicant is required to provide for a particular drug to meet the statutory standards." *Id.*

The NDA must contain: 1) reports of all investigations (preclinical and clinical); 2) a summary of the efficacy data and the safety data; 3) the composition of the drug; 4) methods and facilities used in the manufacture of the drug; 5) drug samples; 6) integrated assessment of benefit/risk; 7) proposed labeling; 8) and postmarket safety and other information concerning the drug's use in foreign markets.

Once the NDA has been submitted, FDA scientists determine whether the data are sufficient to establish that the drug meets FDA's safety and efficacy requirements. A team of physicians and other scientists conduct a careful review of the NDA and prepare detailed reports on their findings. FDA reviewers are all experts in their fields. After intensive assessment by the FDA review team, FDA then issues a letter to the sponsor indicating whether the NDA has been approved, not approved, or is approvable. If it is approvable but not approved, FDA identifies the deficiencies that must be corrected and the additional information required before approval can be reconsidered.

The U.S. drug development process is rigorous and scientifically sound. FDA estimates that of the 1,000 compounds initially identified as having potential as a new drug, five will enter clinical testing in the U.S. Of the five that reach the IND stage, three will reach the NDA stage, and of those, only one will eventually be marketed.

3. Prescription Drug Labeling

Congress specifically provided FDA with the responsibility for assuring that prescription medicines marketed in the United States are safe and effective for use when used in accordance with the approved product label and contains adequate directions for use. 21 U.S.C. § 355(b)(1)(F). As an integral part of the NDA approval process, FDA evaluates and approves the exact language that appears on the package insert. *Id.* In general, a manufacturer must submit a supplement to FDA for approval of "any change in labeling." 21 CFR § 314.70(b)(3). Although a manufacturer can "add or strengthen a contraindication, warning, precaution or adverse reaction" to the label prior to approval of a supplement, the supplement must still be submitted. 21 CFR§ 314.70(c)(2)(i) [CHECK CITE]. FDA maintains strict control over prescription drug labels, and, in my experience, FDA does not compromise on safety issues.

A prescription medicine label is the primary means for FDA and the manufacturer to provide the essential information a health care provider needs to know in order to safely and effectively prescribe a drug to his or her patient. As FDA has stated in the Preamble in January 24, 2006,

> Under the act and FDA regulations, the agency makes approval decisions based not on an abstract estimation of its safety and effectiveness, but rather ona comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended or suggested in the labeling (21 C.F.R. 355(d))...The centerpiece of risk management for prescription drugs generally is the labeling, which reflects thorough FDA review of the pertinent scientific evidence and communicates to healthcare practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively . FDA carefully controls the content of labeling for a prescription drug, because such labeling is the principle tool for educating healthcare professionals about the risks and benefits of the approved product to help ensure safe and effective use. FDA continuously works to evaluate the latest available scientific information to monitor the safety of products and to incorporate information into the products' labeling when appropriate.

71 Fed. Reg. 3922, 3934 (Jan. 24, 2006).

Thus, the label of a prescription medicine is the main mechanism by which FDA and the manufacturer communicate essential information to physicians or other health care providers. The approved label allows the medicine to be used safely and effectively. A draft label is submitted as part of an NDA, and is extensively reviewed and revised by the sponsor and by FDA prior to product approval. Although development of the label is a complex and iterative process between the company and FDA, FDA makes the final determinations on the appearance, content, placement and language of information in the label. The final draft of a product label is based on the best judgment of both the manufacturer and FDA and in accordance with the regulations. Both FDA and the product sponsor review the labeling throughout marketing for possible revisions based on postmarketing safety data or other information.

The labeling requirements in effect during the time Neurontin was under consideration for approval are found in 21 C.F.R. § 201.57. These requirements, which were in effect prior to a recent revision in the format for prescription drug labeling, specified that safety information is to be included in the Contraindications, Warnings, Precautions, and Adverse Events sections of the labeling 21 C.F.R. § 201.57(d) (f).

Additional safety information may found in boxed warnings, but such warnings may only be added to the label when required by FDA. FDA has stated, "[T]o ensure

the significance of boxed warnings in drug labeling, they are permitted only when specifically required by FDA." 44 Fed. Reg. 37434, 37488 (June 26, 1979). FDA has also stated:

> Under § 201.57(e) (21 C.F.R. § 201.57(e)), which lists specific requirements on content and format of labeling for human prescription drugs, the agency has the authority to require a 'boxed' warning on prescription drug packages for special problems, particularly those that may lead to death or serious injury...The agency's policy is to use restraint in requiring warnings to be boxed because overuse of the box will ultimately lead to reducing its effect.

51 Fed. Reg. 43900, 43902 (Dec. 5, 1986). FDA has never suggested or required boxed warnings for the Neurontin label.

4. FDA and Industry Share Responsibility for Review and Revision of Prescription Medicine Labels

Virtually all prescription pharmaceutical product labels undergo changes over time as new information about safety or efficacy becomes available. While all changes to a prescription medicine label must be approved by FDA, there are two mechanisms for obtaining approval of label changes. One is the prior approval mechanism in which a company submits a proposed labeling change to FDA and the proposed change, with supporting data are reviewed, much as an initial review. The change is either approved, not approved, or found to be approvable.

The second mechanism for obtaining a labeling change is known as the "changes being effected" (CBE) provision of 21 C.F.R. § 314.70(c). Although a manufacturer may alter the labeling to add or strengthen a warning or to delete "false, misleading or unsupported indications," in practice most pharmaceutical companies consult with FDA prior to submitting a safety-related CBE supplement. A sponsor may institute a labeling change under the CBE mechanism, but such changes are subject to FDA's finding that the change is not approvable. As stated in the Preamble to FDA's January 24, 2006 change in the format for prescription drug labeling:

> While a sponsor is permitted to add risk information to the [package insert] without first obtaining FDA approval via a CBE supplement, FDA reviews all such submissions and may later deny approval via a CBE supplement, and the labeling and the labeling remains subject to enforcement action if the added information makes the labeling false or misleading under section 502(a) of the Act (21

U.S.C. 352). Thus, in practice, manufacturers typically consult with FDA prior to adding risk information to labeling.

71 Fed. Reg. at 3934

The CBE mechanism is generally used for minor changes in manufacturing or materials and for certain types of safety-related labeling changes. In general these are safety-related changes that add or strengthen a contraindication, warning, precaution, or adverse reaction; add or strengthen instructions about drug abuse, dependence, or over-dosage; add or strengthen information about dosage and administration intended to increase the safe use of the product: or to delete "false, misleading, or unsupported indications for use or claims for effectiveness."

5. Risk/Benefit Assessment

Virtually all prescription medicines have adverse side effects. It is a well accepted principal that the full spectrum of a medicine's effects, both positive and negative are not, and probably cannot, be known at the time of initial marketing. When FDA approves an NDA or sNDA, it has reached a determination that the medicine has been shown to be safe and effective when used in accordance with its approved label. This means that FDA has found that the known benefits of the drug outweigh its known risks when used in accordance with the approved labeling. The benefit risk assessment is a central and ongoing part of the drug approval process involving judgment by FDA reviewers and the sponsor.

6. Post-market safety surveillance and monitoring

After a new drug is approved for marketing, the responsibilities of the sponsor and FDA to assure the continued safety and effectiveness of the prescription medicine are expanded to include post-market safety surveillance and monitoring. Under 21 CFR 314.80, both FDA and the drug sponsor are required to monitor and review all reports of adverse drug experiences or adverse drug events that are reported or otherwise come to the attention of FDA reviewers or the sponsor. Adverse events or adverse drug experiences are any adverse or untoward outcomes associated with the use of a drug in humans, whether the event is considered related to the drug or not (21 CFR 314.80(a)). Adverse events may occur when a prescription drug is used in the professional practice of medicine, in the event of overdose, abuse or withdrawal; or in the event of the failure of the expected pharmacologic action of the drug.

FDA classifies adverse events as expected on unexpected based on the presence of that event in the product label; if a reported adverse event is contained in the approved product label, it is considered to be an 'expected" event. Conversely, if the event is not listed on the current product label, the event is considered to be

"unexpected". Adverse events are also classified as serious or non-serious. A serious event is defined in the regulations (21CFR314.8(a)) as an event that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of a current hospitalization, a persistent or significant disability/incapacity, a congenital anomaly or birth defect, or an important medical event which, based on appropriate medical judgment, is felt to jeopardize the patient or may require medical or surgical interventions to prevent one of the outcomes listed above.

A drug sponsor is required to promptly notify FDA in the event of a serious, unlabeled adverse reaction. In fact, manufacturers have 15 days in which to report new, serious unlabeled adverse events to FDA. Such events may come to the sponsor's attention from reports submitted directly from physicians, pharmacists, consumers, or other sources, from reports in the medical or scientific literature, or from comments to a manufacturer's representative in a health care provider's office. Adverse event reports may come from domestic or foreign sources.

Other reporting requirements include the submission of domestic serious labeled events, domestic non-serious events, in periodic reports as required in 21 CFR314.80(c)(iv)(2) and submission of annual reports as required in 21 CFR314.81(b)(2). Evaluation of reported adverse events must be based on well-established medical and scientific principles and sound clinical judgment.

Based upon my review of the company's postmarketing pharmacovigilence practices, including information provided by Pfizer to FDA after 2004, there is no evidence of a signal for suicide at any time following approval of the NDA in December of 2003. It also appears that no clinical information emerged during the postmarket use of Neurontin that changed the risk/benefit analysis of Neurontin for its labeled uses.

IV. FDA's Initial Approval of Neurontin®

Warner-Lambert/Parke-Davis submitted the Neurontin IND on May 29, 1986. The initial Neurontin NDA, which includes 250 volumes of data, was submitted on January 15, 1992. The FDA approved the NDA on December 30, 1993. Letter from Robert Temple, M.D., Director, Office of Drug Evaluation, FDA, to Parke Davis Pharmaceutical Research (December 30, 1993) ("1993 Approval Letter").

1. Suicide, Depression and Suicidality in the initial NDA

As part of the initial NDA review and approval process, FDA medical officers reviewed safety information available in Integrated Summary of Safety ("ISS") and four safety updates, including the report of a suicide which had occurred in a controlled clinical trial, six months after the patient's discontinuation of Neurontin.

Further, the Integrated Summary of Safety (ISS) specifically addressed episodes of depression, suicidal ideation, and suicide attempt in a stand-alone section titled "Depression." RR-Reg 720-02957, Integrated Summary of Safety, NDA 20-235 at p. 135 (November 19, 1991) ("Epilepsy ISS"). The section noted that "depression is commonly reported as a concurrent illness in the epileptic population" and that suicide attempt among epileptic patients is "estimated to be 4 to 5 times that expected in a nonepileptic population." *Id.*

As required by FDA regulations, Warner-Lambert/Parke-Davis continued to provide safety data on Neurontin in the safety updates prior to approval and in periodic and other reports as required by FDA. These safety updates included information on all patient deaths and serious adverse events. They were provided to FDA in May 1992, November 1992, May 1993, and December 1993. RR-Reg 720-03079, NDA 20-235 (May 29, 1992) ("First Safety Update"); RR-Reg 720-03132, NDA 20-235 (October 29, 1992) ("Second Safety Update"); RR-Reg 720-03236, NDA 20-235 (May 12, 1993) ("Third Safety Update"); RR-Reg 720-03315, NDA 20-235 (December 15, 1992) ("Fourth Safety Update").

In assessing the safety and efficacy of all prescription drug products, FDA relies on the clinical judgment and expertise of its medical officers. Thus, reports of depression, suicidal behavior, and other psychiatric events were considered by FDA clinicians in their evaluation of the risk/benefit profile for Neurontin. For example, Cynthia McCormick, M.D. noted in her initial report (Combined Medical Statistical Review) that one suicide had occurred six months after the patient's last dose of gabapentin and that this was one suicide among the estimated 2,096 subjects exposed to gabapentin that the suicide "occurred long after discontinuation of treatment." Cynthia G. McCormick, M.D., FDA Division of Neuropharmacological Drug Products, Combined Medical-Statistical Review at p 77 (May 1993) ("Medical-Statistical Review"). As reflected on pages 102, 105, 107-09, 114, and 117 of this initial report, Dr. McCormick evaluated the reports of depression, suicidal ideation, and suicide attempt reported during the clinical trials. *Id.* However, she concluded that the clinical trial data did not demonstrate an increased risk for depression or suicidal behavior among the Neurontin treated patients. In fact, there was a higher percentage of "psychobiologic events" reported for patients on placebo than those receiving Neurontin.

In Dr. McCormick's review of the Fourth Safety Update, she noted that "there is a higher incidence of depression among epileptics with partial seizures as compared to the general population." Cynthia G. McCormick, M.D., FDA Division of Neuropharmacological Drug Products, Review and Evaluation of Safety Update #4 at p. 8 (December 28, 1993) ("FDA Review of Safety Update #4"). Cynthia Dr. McCormick also stated that "one cannot determine based on the available data, largely uncontrolled, whether the reports here represent an increase in incidence or intensity of

depression compared to that which is expected." *Id.* Dr. McCormick evaluated the full spectrum of adverse events, including episodes of depression and suicidal behavior, before concluding that Neurontin was safe and effective and should be approved for marketing.

Episodes of depression and suicide were also evaluated by Dr. McCormick's supervisor, Dr. Russell Katz. In his Supervisory Overview report, Dr. Katz pointed out that the only suicide had occurred "after having been off drug for a considerable time." Russell Katz, M.D., FDA Division of Neuropharmacological Drug Products, Supervisory Overview of Safety and Efficacy Data for NDA 20-235 at pp. 13-15 (October 11, 1993). Like Dr. McCormick, Dr. Katz did not suggest that gabapentin increased the risk for depression or suicidal behavior. Dr. Katz, who is currently the Director of the Neuropharmacological Drug Products Division, agreed with Dr. McCormick's conclusion that Neurontin was safe and effective for its intended use and should be approved. Dr. Katz's supervisor at the time, Dr. Paul Leber, Director of the Neuropharmacological Drug Products Division, agreed with Dr. Katz's and Dr. McCormick's recommendations regarding gabapentin's safety and efficacy. His report raised no concern about depression or suicidal behavior.

2. Peripheral and Central Nervous System Advisory Committee

Gabapentin was a new molecular entity and so it was brought before the Peripheral and Central Nervous System Advisory Committee on December 15, 1992. Prior to the meeting, the Advisory Committee members received a set of briefing materials, which included a draft of Dr. McCormick's medical officer's review. During the course of the meeting, Dr. McCormick provided a summary of her clinical assessment of the safety and efficacy of Neurontin. Transcript of Peripheral and Central Nervous System Drugs Advisory Committee, December 15, 1992, at pp. 18-61. ("PCNS Advisory Committee Meeting"). Included in Dr. McCormick's presentation was a discussion of the data on suicidal behavior and depression. Specifically, Dr. McCormick noted the suicide that had occurred six months after discontinuation of Neurontin. *Id.* at p. 43. Dr. McCormick also noted, among other things, that there had been two suicide attempts among 2,048 clinical trial patients treated with Neurontin. *Id.* at p. 52. She also noted that in controlled and uncontrolled studies, 5.3 percent of Neurontin exposed patients had reported depression, including seven serious adverse events of depression and nine patients withdrawn because of depression, some of whom had suicidal ideation. *Id.* at pp. 55, 58.

At no point during her presentation to the Advisory Committee did Dr. McCormick suggest that Neurontin causes or increases the risk for developing depression or suicidal behavior. With respect to depression, Dr. McCormick noted that "numerous examples were found on a spot check among case report forms where patients

developed treatment-emergent depression, pharmacological intervention was required, and a report of a serious adverse event was not made. Indeed, it wasn't required." *Id.* at p 59.

After considering both safety and efficacy data, including the data on depression and suicide, the Advisory Committee voted unanimously to recommend approval of Neurontin. *Id.* at 126. At no point did the Advisory Committee members suggest that there was an increased risk for suicide or suicidal ideation with Neurontin use.

3. Neurontin® Label approved December 30, 1993

FDA had substantial involvement in developing the text of the Neurontin label approved on December 30, 1993. FDA correspondence and Warner-Lambert records of contact reflect at least 109 communications between Warner-Lambert and the FDA and 140 questions sent by FDA to Warner-Lambert. Robert Temple, M.D., Director, FDA Office of Drug Evaluation (December 21, 1993) WLC_CBU_119980 ("1993 FDA Approvable Letter"). Among these records of contact is a record concerning a meeting at FDA on January 28, 1993, attended by Jan Turner from Warner-Lambert and Dr. McCormick and Nancy Chamberlain from FDA. Record of FDA Contact (January 28, 1993) Pfizer_LAlphs_0087185. During this meeting, the FDA approved Warner-Lambert's proposal to modify certain COSTART preferred terms and also approved the sponsor's proposal to include rare adverse events in the "Other Adverse Events" subsection.

FDA's significant involvement in developing the package insert is also reflected in a record of contact following a phone conversation between officials from FDA and Warner-Lambert on October 6, 1993. Record of FDA Contact (October 6, 1993) WLC_JTurner_000717. The record of contact notes that FDA's delay in approving the NDA is because the agency is "fine tuning the labeling. They are reviewing every word . . . ." On October 15, 1993, FDA telephoned Warner-Lambert to request revisions to a table regarding efficacy data and a table regarding adverse events. Record of FDA Contact (October 15, 1993) WLC_JTurner_000688. FDA also asked that "convulsions" and "CNS Tumors" be added to the "Nervous System" section. On October 19, 1993, FDA asked Warner-Lambert to add back in the rare adverse events under the "Other Adverse Events" subsection. Record of FDA Contact (October 19, 1993) WLC_JTurner_000694. Rare events had earlier been removed from the package insert based on guidance from Dr. Robert Temple, Director of the Office of Drug Evaluation. WLC_JTurner_001685.

In December of 1993, there were a number of telephone conferences between FDA and Warner-Lambert regarding the Neurontin label. These calls included discussions regarding revising the package insert to include warnings about status

epilepticus and sudden and unexplained death (December 22, 1993), whether any events listed in the "Other Adverse Events" subsection should be moved to a different frequency category (December 27, 1993), revisions to the warnings regarding tumorigenic potential (December 29, 1993), and other changes to the preclinical pharmacology and toxicology sections (December 30, 1993). Records of FDA Contact, WLC_JTurner_000813-000828. At no time during these conferences did FDA request or require changes to the label regarding suicide, suicidal behavior, depression, or other psychiatric-related events be modified or moved to a different frequency category. On December 30, 1993, FDA approved the NDA and attached final approved label. As noted in the FDA's approval letter, dated December 30, 1993, the FDA required that the final printed label ("FPL") be identical to the draft labeling the FDA enclosed with its approval letter.

Prior to the revisions to the format of prescription drug labeling, published on January 24, 2006, adverse events were characterized in product labels as frequent (occurring 1/100 or more clinical trial participants), infrequent (occurring in between 1/100 to 1/1000 clinical trial participants), or rare (occurring in fewer than 1/1000 participants). 21 C.F.R. § 201.57(g), In the Neurontin label approved December 30, 1993, "suicidal" was listed as an infrequent event and "suicide gesture" was listed as a rare event. Neurontin U.S.P.I. (1993). The term "suicidal", a term from Warner-Lambert's modified COSTART dictionary, included the investigator-reported terms of attempted suicide and suicide ideation. Appendix B-1, Fourth Safety Update at p. 46. (November 16, 1993). "Suicide gesture" from this same modified COSTART dictionary, encompassed reports of self-injurious behavior without fatal intent and included the investigator-reported terms such as suicide gesture and wrist slashing gesture. *Id.* at 47. Both "suicidal" and "suicide gesture" were in Warner-Lambert's modified COSTART dictionary, which was authorized by FDA. The preferred terminology in FDA's COSTART dictionary for suicide attempt, suicide gesture, and suicide was "Overdose intent". Coding Symbols for Thesaurus of Adverse Reaction Terms, FDA (Second ed. 1985). However, not all suicide attempts involve overdose and not all overdoses are suicide attempts, therefore the Warner-Lambert modification was appropriate given the constraints of the COSTART dictionary terminology.

As noted above, data from the adult epilepsy ISS, related safety updates, and FDA clinical reviews confirms that suicidal adverse events were infrequent and that suicide gesture events were rare Given the background rate of suicidal episodes in patients with epilepsy and the low frequency of suicidal adverse events reported in the clinical studies, it is my opinion that the FDA and Warner-Lambert appropriately listed the data regarding suicidal adverse events and suicide gesture in the "Other Adverse Events Observed During All Clinical Trials" subsection. The final approved label also appropriately identified data on all other psychiatric-related terms, including episodes of

depression, psychosis, and thinking abnormal. The final printed label that was attached to FDA's approval letter dated December 30,1993 used the modified COSTART terms "suicidal" and "suicidal gesture" to describe the adverse events involving suicidal behavior that occurred in the clinical trials. From the time of initial approval of the Neurontin NDA, the Neurontin package insert adequately described the occurrence of suicidal behavior that had been reported to the company during the clinical trials, in accordance with FDA regulations and policies.

4. Warnings, Precautions, and Contraindications

It is my opinion that addressing suicidal behavior or other psychiatric-related events in a warning, precaution, contraindication, or other prominent listing in the Neurontin package insert is not necessary or appropriate.. A warning or other prominent listing on these events would misstate the clinical trial data and mischaracterize the risks associated with Neurontin. In addition, a warning or other prominent listing could harm the public health by discouraging the use of Neurontin by patients who would otherwise benefit from the use of the drug.

The FDA is careful to limit the use of boxed warnings to clearly appropriate situations, thereby avoiding a proliferation of warnings that will dilute their impact. FDA has stated, "[T]o ensure the significance of boxed warnings in drug labeling, they are permitted only when specifically required by FDA." 44 Fed. Reg. at 37488. In addition, FDA is concerned that patients will be discouraged from using potentially useful medications because of inappropriate warnings, precautions, or contraindications. Language in the package inserts for other prescription medications cited in the Blume report have no bearing on the need to change the Neurontin package insert to include information including warnings, precautions or contraindications concerning suicidal behavior or depression.

5. FDA's Approval of Neurontin® for Postherpetic Neuralgia

Neurontin underwent additional regulatory review when Pfizer submitted an NDA in August of 2001 for Neurontin in the management of neuropathic pain. Letter from Drusilla Scott, Ph.D., Pfizer to FDA (August 6, 2001) Pfizer_AGarrity_0002519. The neuropathic pain indication was revised to post-herpetic neuralgia ("PHN") in October 2001. Letter from Drusilla Scott, Ph.D., Pfizer to FDA (October 22, 2001) Pfizer_LKnapp_0025817. FDA's clinical reviewers carefully evaluated the clinical safety and effectiveness information submitted in this NDA. The clinical review of these data was performed by Sharon Hertz, M.D., and Dr. McCormick submitted her own evaluation of the post-herpetic neuralgia (PHN) submission as the "Division Director Review and Basis for Approval Action."

As with the previous NDA for the treatment of epilepsy, Pfizer's PHN regulatory submissions included data on adverse events reported during the neuropathic pain studies. In the PHN ISS, dated December 13, 2001, Pfizer provided cumulative data and patient narratives for all reports of deaths and serious adverse events resulting in patient withdrawal from the controlled trials. RR-Reg 720-30135, PHN Integrated Summary of Safety, (December 13, 2001) ("PHN ISS"). The data from the two controlled trials in PHN and the five controlled trials for neuropathic pain indicated that more patients randomized to placebo reported serious depression than patients randomized to Neurontin. Sharon Hertz, M.D., FDA Division of Anesthetic, Critical Care, and Addiction Drug Products at Table 7.20 (May 24, 2002) ("Dr. Hertz Clinical Review"). Specifically, 2.2 percent of placebo patients in the neuropathic pain studies reported depression as a serious adverse event as compared to 1.3 percent of patients on Neurontin. *Id.* The same held true for reported episodes of depression leading to patient withdrawal. PHN ISS at Table 24.

Dr. Sharon Hertz's Medical Officer Review paid appropriate attention to data on depression and suicide attempt. In her report , she discusses the sole report of suicide attempt of a patient in the neuropathic pain clinical trials. Dr. Hertz Clinical Review at 66. Dr. Hertz remarked on the fact that the ingestion was only 4500 mg of Neurontin; Dr. Hertz appropriately attributed the somnolence reported in that case as being the drug-related event, not the overdose itself. *Id.*

Dr. Hertz further summarized the depression data in a chart identifying all serious adverse events reported in the neuropathic pain and epilepsy studies. In addition to the summary data above indicating a higher rate of serious reports of depression in placebo patients than in the Neurontin patients, Dr. Hertz's chart also provides a comparison of serious depression events reported from all controlled epilepsy and neuropathic pain trials. *Id.* at Table 7.20. The results of this comparison again show a numerically higher rate of depression reported among placebo patients than among patients on Neurontin; 1.7 percent of patients on placebo reporting depression as compared to 1.5 percent of Neurontin patients. *Id.*

Furthermore, Dr. McCormick's "Division Director Review and Basis for Approval Action" dated May 22, 2002 raises no concerns about depression or suicidal adverse events and states "there has been adequate demonstration of safety and effectiveness of Neurontin in the treatment of postherpetic neuralgia". Cynthia McCormick, M.D., Director, FDA Division of Anesthetic, Critical Care, and Addiction Drug Products, Division Director Review and Basis for Approval Action (May 22, 2002) ("Division Director Review").

Both Drs. Hertz and McCormick concluded that Neurontin's safety and efficacy in treating patients with PHN was established in two adequate and well-controlled clinical

trials. Accordingly, on May 24, 2002, FDA approved the use of Neurontin in the management of postherpetic neuralgia, when used in accordance with the approved labeling. Letter from Cynthia McCormick, M.D., Director, FDA Division of Anesthetic, Critical Care, and Addiction Drug Products, to Drusilla Scott (May 24, 2002). Again, the approved package insert for the postherpetic neuralgia indication adequately disclosed information concerning suicidal behavior in accordance with FDA regulations and policies.

6. Labeling Change in December 2005

In December 2005, Pfizer agreed to update the Neurontin package insert by replacing the terms "suicidal" and "suicide gesture" with the terms "suicide attempt" (infrequent) and "suicide" (rare). Pfizer_Regulatory_000031; Neurontin U.S.P.I. (December 2005). Both FDA and Plaintiffs' own retained expert, Cheryl Blume, considered these changes to be "minor." Pfizer_Regulatory_000003; Report of Cheryl Blume, Ph.D. at paragraphs 214 and 287. Additionally, replacing the Warner-Lambert modified COSTART terms with preferred terms from the MedDRA Dictionary in the "Other Adverse Events" subsection was appropriate. FDA did not request any other labeling changes. That the FDA did not require further revisions (such as a Black Box warning or any warning at all) or request the issuance of a "Dear Healthcare Provider" letter, suggests that the FDA did not believe there was an increased risk for suicide or suicidal behavior in patients using Neurontin.

The purpose of providing safety information in the label is to inform prescribers and patients of the most important information related to a particular medicine. It is my opinion that the Neurontin package inserts before and after December 2005 adequately informed prescribers of the risks and benefits of Neurontin, particularly with respect to suicide-related events. For these reasons, I believe the Neurontin U.S. package insert at all times relevant to this litigation adequately and appropriately disclosed the potential risks of Neurontin, including suicidal thinking and behavior.

7. FDA Involvement with Neurontin Labeling

It is clear from the record of FDA's evaluation of the various regulatory submissions, that the agency understood the labeling issues associated with Neurontin and suicidal behavior and depression in the clinical trials. It is also clear that FDA was intimately involved with the drafting of the Neurontin label, not only at the time of the initial approval, but also for subsequent submissions to the NDA. FDA's substantial involvement with the development of the Neurontin label is confirmed by Dr. McCormick in her affidavit, which I have reviewed. Her affidavit is consistent with my review of these documents in the record. I agree with Dr. McCormick's clinical assessment that "given the relatively low frequency of suicidal adverse events reported in the clinical

trials and the high background rate of suicidal behavior in patients with epilepsy . . . it would have been inappropriate to address suicidal behavior in the warnings, precautions, or contraindications sections." Affidavit of Cynthia McCormick, M.D. at p. 9 (September 13, 2007). I also agree with Dr. McCormick's clinical assessment that "the final printed labeling approved by FDA in May 2002 appropriately and accurately identified the data on psychiatric-related events in the neuropathic pain clinical trials. *Id.* at p. 15.

V.. Plaintiff"s Expert Cheryl Blume, Ph.D.

I have reviewed the report submitted by plaintiffs' retained expert, Cheryl Blume, Ph.D, as well as her deposition testimony. There are a number of errors and misconceptions in both her expert report and in her testimony at deposition. For instance, she alleges that Pfizer failed to acknowledge "psychobiologic" adverse events that she claims indicate significant adverse events predictive of suicidal behavior. There is no evidence that the clinical reviewers at FDA in any way considered this disparate group of adverse events as predictive of suicide or suicidality. Nor is there evidence that such events were ignored by the company or FDA. Dr. Blume provides no discernable scientific rationale for her assertions about any of the "psychobiologic" events, such as depersonalization, which she claims are somehow predicative of an increased risk for depression, suicidal ideation, suicidal behavior or suicide. Diagnosis of a major depressive episode (according to Cecil's Textbook of Medicine, 20th edition, p. 1999) can include suicidal ideation, suicidal attempt, or recurrent thoughts of dying as one of the diagnostic criteria, under certain circumstances. The numerous events listed by Dr. Blume have not been shown to be predictive of depression or suicidal behavior.

Dr. Blume also alleges that Pfizer failed to include information in the Neurontin label about the effects of gabapentin on monoamine neurotransmitters within the central nervous system. Blume Report at p. 184. A review of the draft labels submitted to FDA by Warner-Lambert prior to the initial approval of Neurontin indicates that this allegation misrepresents the facts. The January 1992, draft label submitted by Warner-Lambert with the Neurontin NDA includes a statement in the Mechanism of Action section submission that "Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*." Gabapentin Annotated Package Insert, NDA 20-235 at p. 3 (January 1992). This sentence appears in a number of subsequent drafts of the product label before being removed by FDA in December 1993. Neurontin Revised Package Insert (January 26, 1993) WLC_CBU_118839; Neurontin Revised Package Insert (September 2, 1993) WLC_CBU_122636.

Similar language regarding mechanism of action was included in the draft label submitted as part of the PHN NDA. The draft labels provided to FDA in August 2001 and January 2002, included the following: "Gabapentin reduces the stimulated release of noradrenaline, dopamine, and glutamate under laboratory conditions. Annotated Neurontin Labeling at (August 2001) Pfizer_LAlphs_0080557; Neurontin Revised

Package Insert (January 2001) Pfizer_LKnapp_0066074. Gabapentin administration to humans increases the total brain content of GABA after a single dose. However the relevance of these findings to clinical use is not yet clear." *Id.* Again FDA deleted this language during its review of the draft package insert prior to approving Neurontin for the treatment of post-herpetic neuralgia. FDA Revised Draft of Neurontin U.S. Package Insert, FDA, Division of Neuropharmacology, HFD-120 (May 16, 2002) Pfizer_LCastro_0011566. It is my opinion that FDA would not have removed this language if FDA scientists and clinicians believed it had any relevance to the safe or effective use of the product. I believe Dr. Blume is mistaken in her assertion that Neurontin's possible effects on transmitters within the central nervous system has any bearing on the safety of Neurontin, an opinion that is supported by FDA's deletion of this language from the Neurontin labels. After May of 2002, there has been no reason, or scientific basis, for Pfizer to resubmit similar labeling to FDA on this issue.

I have reviewed the reported methods and data upon which Dr. Blume appears to base the opinions she offers in her report. At a number of places in her report, Dr. Blume presents what are essentially line listings of adverse events, and thendraws inferences and conclusions from those line listings. I see no evidence that she preformed any analyses to determine if the differences she claims to have identified in rates of events between the comparison groups (treated patients or placebo-treated patients) are more likely to be real differences or simply due to chance alone. The types of comparisons she makes, comparing numbers of events in one population and numbers of similar events in a different population, in the absence of any statistical analyses, could not be relied upon as demonstrating true differences between the Neurontin-exposed population and the placebo-exposed population, much less establishing causation. The "analyses" she reports are not consistent with generally accepted epidemiological principles and are not reliable as measurements of the association between those events and an exposure of interest. Such comparisons not used by epidemiologists, clinical scientists or regulatory agencies, such as FDA, to evaluate whether a medicine is causally associated with an adverse event. The presentation of lists of adverse events, as set forth in the Blume report, does not contribute to the assessment of an association between Neurontin and suicide.

Dr. Blume opines that reports of positive "dechallenge" and "rechallenge" events provide support for her claim that Neurontin plays a causal role in the occurrence of suicide or suicidal behavior among patients exposed to the drug. A positive dechallenge occurs when a patient is withdrawn from a drug suspected as associated with a particular adverse event and the adverse event regresses or disappears. A positive rechallenge means the suspect drug is re-introduced and the event recurs. Dechallenge and rechallenge are most meaningful when the event reported is an objectively documented or measured event, such as abnormal kidney function tests that

improve on discontinuation of a suspect drug and then become abnormal again when the drug is re-introduced. Thus, dechallenge or rechallenge data are most useful in measuring changes in an objective sign or laboratory test rather than in the case of subjective events. The dechallenge and dechallenge/rechallenge reports involving highly subjective adverse experiences like several of those cited by Dr. Blume, are subject to biases which render them more difficult to interpret than are changes in.objective adverse events upon dechallenge alone or dechallenge and then rechallenge. Girard, M., "Oral Provocation Limitations," Br. J. Clin. Pharmac. (1987) 23, 73-79.

In addition, the "psychobiological" events discussed by Dr. Blume are not rare in the patient populations exposed to Neurontin in the absence of Neurontin exposure. Therefore, based on the data used and the methodologies proposed by Dr. Blume, the dechallenge/rechallenge data from which she infers a causal association between Neurontin and suicide or suicidal behavior could not be considered a reliable basis from which to draw such inferences.

Dr. Blume testified at her deposition that the Neurontin package insert should have contained warnings or other labeling changes that would discourage physicians from prescribing Neurontin based on safety issues she has identified. Blume Deposition at 216, 682. She also noted in her report that Pfizer should have warned healthcare professionals about a possible lack of efficacy in certain off-label indications. Blume Report at 9. I do not agree with these opinions.

Under 21 C.F.R. § 201.57(e)(2005) "{i}f there is a common belief that the drug may be effective for a certain use of if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows the drug is ineffective" FDA may require that the label state that there is a lack of evidence demonstrating efficacy for that use. In the recently published revisions to the format for prescription drug labels, FDA may require the addition of warnings to a package insert if it believes the medication poses an increased risk in certain patient populations using the drug off-label. Section 201.57(e) (2006) states, in part, that "A specific warning relating to a use not provided for under the 'Indications and Usage' section of the labeling may be required by the Food and Drug Administration if the drug is commonly prescribed for a disease or condition, and there is lack of substantial evidence of effectiveness for that disease or condition, and such usage is associated with serious risk or hazard." 21 C.F.R. § 201.57(c)(6)(i)(2006). In addition, Section 201.57(c)(3)(iii) states, in part, that "If there is a common belief that the drug may be effective for a certain use or if there a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require

that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition." 21 C.F.R. § 201.57(c)(2)(ii)(2006).

Dr. Blume testified that FDA has known for at least several years that physicians were prescribing Neurontin for off-label indications. Blume deposition at 694. First, FDA does not regulate the practice of medicine, meaning that once a product is approved for marketing in the U.S., prescribers are permitted to prescribe or use the product as they feel is in their patients' best interests. Furthermore, had FDA believed that Neurontin posed an increased risk of injury only in certain patient populations using the medication off-label, it had the full authority to require Pfizer to include in the Neurontin labeling a specific warning regarding efficacy or safety concerns associated with off-label uses. 21 C.F.R. § 201.57(e) (April 2002). To date, FDA has not requested that this type of a warning be added to the Neurontin labeling and it is my opinion that such a warning would have been inappropriate and unsupported by the available clinical data.

Dr. Blume's report sets forth a purported "Proportional Reporting Rate" ("PRR") of the FDA AERS database in support of her contention that the postmarketing surveillance data revealed a "signal" for suicide. The analysis presented in Dr. Blume's report is not a PRR. Rather, Dr. Blume merely presents the percentage of suicide events for each drug relative to the total number of adverse events for that drug. This is not the generally accepted method for calculating a PRR, which would require an analysis of the entire AERS database. Even if her analysis were a generally accepted-type of PRR, Dr, Blume has not followed generally accepted methodology in interpreting the information. As stated by Dr. Brian Strom (who Dr. Blume has acknowledged as an authority in the field of pharmacoempidemiology), "...true signals should emerge from clinical judgment and that statistical algorithms, such as PRRs, should be used as supplements to clinical and epidemiological judgment, not replacements." Brian L. Strom, "Evaluation of Suspected Adverse Drug Reactions – Reply," JAMA 293:1324 – 1325 (2005).

Dr. Blume has not applied reliable methodologies for analyzing adverse event data or interpreting her data analyses. Indeed, because she is neither a clinician nor an epidemiologist, she is not qualified to apply clinical or epidemiological judgment to her purported PRR results. It is well established that:

> Disproportionality measures are formal statistical analyses of poor, incomplete, and based data (i.e., SRS data). No matter how sophisticated, formal analyses of such data can easily be misleading; they cannot correct for imperfections in the data source. Proper interpretation also requires clinical judgment before one even considers there to be a signal. However, the use of such statistical

algorithms of spontaneously reported data as if the algorithms tested hypotheses, is incorrect. Id.

In opining on the question of whether Neurontin causes suicidal behavior, Dr. Blume appears to combine uncontrolled clinical data (i.e., rechallenge event from an uncontrolled trial), adverse event reports and both *in vitro* laboratory data and *in vivo* data to conclude that there is a causal association between Neurontin and suicide. I can discern no scientific basis for the use of such disparate data, all of which was reviewed by FDA, and no valid basis for the use of these data to arrive at a conclusion that Neurontin causes suicide or suicidal behavior during the course of its clinical use This speculative use of preclinical and clinical data is not a methodology supported by any scientific data of which I am aware that links the gabapentin laboratory and preclinical data to the clinical outcome of suicide or suicidal behavior.

Blume's Proposed Label Changes:

Dr. Blume, in her report, proposed the following label changes:

> *"Incidences of positive dechallenge/rechallenge events have been documented in clinical trials involving gabapentin. Dechallenge events include suicidal ideation, depression and hostility. In addition, a positive rechallenge event was documented in one patient (depression). The temporal relationship between the tapering/discontinuation of gabapentin therapy and the resolution of the depression and suicidal ideation events in this patient suggests that gabapentin precipitated these events."* Blume Report at pp. 195-96.

FDA had the dechallenge/rechallenge reports upon which Dr. Blume bases her proposed language for the Neurontin label. At no time did FDA recommend or insert such language in any draft label. Since FDA is the expert agency designated by Congress to ensure the safety and effectiveness of medical products on the U.S. market, including prescription pharmaceuticals, it would appear that such language was not appropriate for the agency to discharge its public health obligation.

> *"Neurontin reduces the stimulated release of noradrenaline, dopamine, and glutamate under certain laboratory conditions. Gabapentin administration increases the total brain content of GABA after a single dose. However, the relevance of these findings to clinical use is not yet clear."* Blume Report at 196.

Dr. Blume's proposed changes to the Neurontin label are apparently based upon *in vitro* laboratory experiments, which Pfizer sought to include, but FDA repeatedly removed,

from the Neurontin package insert. There is no logic in Pfizer re-submitting this language concerning the mechanism of action of Neurontin for FDA consideration given that FDA has already twice considered and rejected this labeling.

> *"Neurontin slightly reduces the release of excitatory neurotransmitters (e.g. serotonin, norepinephrine) in vitro. A reduced release of excitatory neurotransmitters in the brain may contribute to depression and suicidal behavior."* Blume Report at 196.

There is no scientific basis for this assertion. There are no data to support the proposition that a "reduced release of excitatory neurotransmitters in the brain [*i.e.*, changes in release measured *in vitro* in animal tissue under specific laboratory conditions] may contribute to depression or suicidal behavior." To date, there have been no data produced that establishes a causal relationship between any pharmacological property of gabapentin and depression or suicidal behavior in humans.

> *"Patients of all ages who are started on Neurontin should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber."* Blume Report at 196.

FDA has been provided with, and has carefully reviewed, clinical trial and postmarketing data regarding suicide and Neurontin. FDA has specifically addressed the Neurontin label as it relates to suicide. Had FDA determined a need for the language proposed by Dr. Blume to assure the safe and effective use of the medication, it would have required such a change to the label, as it has for other psychotropic compounds where an association was suggested between exposure and suicidality. The pertinent data for gabapentin, in contrast, do not suggestion such an association.

> *"Depression and suicidal behavior (ideation, attempt, and completed suicide) have been reported to occur in patients receiving Neurontin. Patients treated with Neurontin should be advised to report immediately any symptoms of depression and/or suicidal ideation to their prescribing physicians. If a patient develops depression, cessation of Neurontin therapy should be considered."* Blume Report at 196.

Again, FDA has been provided with and reviewed clinical trial and postmarket safety data as regards to suicide and Neurontin. FDA specifically addressed suicide in the Neurontin label and has neither suggested nor required the type of warning proposed by Dr. Blume to be included in any label. Had FDA determined the need for such language to be included in the label, it could have communicated this request to Warner-

Lambert/Pfizer and there is no evidence that such communication ever occurred. As noted above, depression did not occur in a significantly greater number of subjects on Neurontin as compared to those on placebo.

> *"A variety of abnormal thinking and behavior changes have been reported to occur in association with the use of Neurontin. Some of these changes may be characterized by decreased inhibition (e.g. aggressiveness), depersonalization. In patients with pre-existing psychiatric conditions, worsening of depression, including suicidal thinking has been reported in association with the use of Neurontin. It can rarely be determined with certainty whether a particular instance of abnormal behaviors listed above is drug induced, spontaneous in origin, or a result of an underlying psychiatric or physical disorder. Nonetheless, the emergence of any new behavior sign or symptom of concern requires careful and immediate evaluation."* Blume Report at 196.

This labeling change is no more appropriate than the previous changes proposed by Dr. Blume and addressed in this report. FDA has reviewed the data upon which Dr. Blume bases this proposed change. There is no evidence that FDA, having reviewed the Neurontin safety data a second time before approving the PHN indication, considered the need to add this or similar language to the Neurontin label. Furthermore, there is no scientific or clinical basis for the alleged association between Dr. Blume's "psychobiological events" and an increased risk for suicide. Adding risk information not founded on good science or clinical reasoning could serve only to "erode and disrupt the representation of benefits and risks that prescribers need to make appropriate judgments about drug use. Exaggeration of risk could discourage appropriate use of a beneficial drug" and is therefore not appropriate. 71 Fed. Reg. at 3935.

VI. Citizen's Petition

A citizen's petition was filed on May 17, 2004 alleging that Neurontin was responsible for suicides among persons exposed to it for a variety of approved and unapproved uses. Keith Altman, Finkelstein & Partners, Citizen Petition (May 17, 2004). The petition, submitted by the law firm of Finkelstein & Partners, requested that "FDA require the manufacturer of Neurontin to amplify the Neurontin labeling to specifically warn prescribers and healthcare professionals of the escalating number of postmarketing reports of completed suicides by patients receiving Neurontin for both its labeled and unlabeled indications." *Id.* Prior to the submission of the Citizen's Petition, one or more members of the law firm had meetings with FDA and Dr. Russell Katz regarding this purported association between Neurontin and suicide. Letter from Andrew Finkelstein, Finkelstein & Partners, to FDA (March 21, 2005) at pp. 2-3; Letter

from Dr. Russell Katz, Director, FDA Division of Neuropharmacology, to Andrew Finkelstein at p. 1 (April 12, 2005).

On April 26, 2004, after having had several meetings with the attorneys from Finkelstein and Partners, FDA asked Pfizer to perform a comprehensive search of gabapentin clinical trials and postmarketing databases for cases of suicide and suicide attempt. FDA Contact Report (April 26, 2004) Pfizer_BParsons_0141815. In a letter dated November 5, 2004, FDA wrote to Finkelstein and Partners, "FDA has been unable to reach a decision on your petition because it raises issues that require additional review and analysis by the agency." Letter from Jane Axelrad, Associate Director for Policy, FDA, to Keith Altman, Finkelstein & Partners (November 5, 2004).

In September 2004, in response to the request from FDA, Pfizer submitted the results of a search for suicide-related events in 92 Phase II through IV clinical studies that had been included in Pfizer/Warner-Lambert's U.S. regulatory submissions. Response to FDA: Neurontin (September 9, 2004) Pfizer_MPatel_0039110. The analysis revealed two completed suicides and 12 suicide attempts out of a population of over 9,000 patients and 4,495 patient-years of exposure, most of whom were at increased risk for suicide and suicidal behavior due to their medical conditions. *Id.* at p. 2. Neither of the completed suicides was considered related to Neurontin. *Id.* at pp. 2, 39, 44. In fact, one of the suicides involved a patient who committed suicide 6 months after she had stopped taking Neurontin. *Id.* at p. 44.

These data also showed that eleven of the 12 patients who attempted suicide were being treated for epilepsy, and the other event involved a patient suffering from painful diabetic neuropathy. *Id.* at pp. 2, 32. As discussed below in greater length, patients with these illnesses are known to have a higher incidence of suicide-related events than the general population. There were no suicide-related events reported by any patients from the Neurontin psychiatric disorder studies.

Two months later, in November 2004, Pfizer submitted to FDA the results of its search for cases of suicide and suicide attempts in 55 Phase I studies. Response to FDA Regarding Suicide and Suicide Attempt in Neurontin Clinical Trials – Phase 1 Studies (November 19, 2004) Pfizer_MPatel_0045143. There were no cases of suicide or suicide attempt in any of the controlled or un-controlled Phase I studies involving healthy volunteers or patients. *Id.*

Overall, the data submitted in September and November of 2004 regarding suicide and suicide attempt from the clinical trials and the postmarketing data failed to signal as association, let alone a causal association between Neurontin and suicidal behavior. Further, the clinical trial findings on completed and attempted suicide are consistent with the medical literature, which indicates that the background rates for

suicide are higher in patient populations with epilepsy, pain and psychiatric disorders than in the general population.

On March 21, 2005, Finkelstein and Partners sent 258 MedWatch forms to FDA concerning patients who had committed suicide while on Neurontin. Letter from Andrew Finkelstein, Finkelstein & Partners, to FDA (March 21, 2005). These adverse event reports were presumably provided directly to FDA by the Finkelstein law firm and not via expedited reports from Pfizer. The addition of a large number of reports of this type into the AERS database produces a significant bias, which would preclude an analysis of the database for a potential signal.

In a letter dated April 12, 2005, FDA wrote to Mr. Finkelstein stating that FDA was "taking this matter very seriously, and have given it a great deal of attention since you first contacted us." Letter from Dr. Russell Katz, Director, FDA Division of Neuropharmacology, to Andrew Finkelstein at p. 1 (April 12, 2005). FDA also stated, "We would also like you to know that in part because of the concerns you have raised, we have asked the sponsors of all drugs approved to treat epilepsy to re-analyze their controlled trials databases to examine the questions of drug-induced suicide and/or suicidality." Letter from Dr. Russell Katz, Director, FDA Division of Neuropharmacology, to Andrew Finkelstein at p. 2 (April 12, 2005).

In June of 2006, at the request of the FDA and using FDA inclusion criteria, Pfizer submitted the results of its evaluation of Neurontin clinical trial data for "possibly suicide-related adverse events." Response to FDA Suicidality Request (June 22, 2006) Pfizer_MEvertsz_0079431. This analysis included 8829 patients, among whom 336 cases of "possibly suicide-related" adverse events were identified. *Id.* at 3. A further analysis and classification of the 336 possible cases revealed no cases of completed suicide, no cases of attempted suicide and no cases of "preparatory acts towards imminent suicidal behavior" among Neurontin users. *Id.* at 4. Pfizer wrote, ""[T]he currently submitted dated provides further support for the conclusion that Neurontin neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicide gesture and suicide ideation." *Id.* The June 2006 submission is consistent with the September and November 2004 submissions in that all three submissions support the conclusion that there is no reliable evidence of an increased risk of suicidal thinking or behavior with Neurontin.

Since 2004, despite repeated efforts by plaintiffs' attorneys to compel specific labeling changes to the Neurontin label, FDA has not sought substantive changes regarding the risk of suicide or other psychiatric adverse events for the Neurontin label.FDA's consideration of both the clinical trial and postmarketing surveillance data has not resulted in any substantive action FDA to change the Neurontin label such as warnings, contraindications or precautions based on suicide adverse events. As of the

date of this report, the only reasonable conclusion is that FDA, in the exercise of its statutory duty to protect the public health, has not found it necessary to change the Neurontin package insert, as suggested by Dr. Blume in her report.

Further, it is my opinion that if FDA had found that the data submitted since 2004 supported a finding of an increased risk for suicidal behaviors associated with the use of Neurontin, FDA would have taken the necessary steps to promptly seek a labeling change. Neither the FDA nor any regulatory authority in the world of which I am aware has found that Neurontin causes suicide. FDA's postion is consistent with my review of the available evidence.

VII. Background Rates of Suicide in Patients with Chronic Pain, Epilepsy, and Psychiatric Illnesses

Epidemiologic data show that the patient populations who were studied in gabapentin clinical trials and who were prescribed Neurontin in clinical settings have a higher rate of suicide than the general population. These populations include patients with epilepsy, pain disorders, and psychiatric illnesses such as anxiety and bipolar disorder.

Regarding bipolar disorder, published data show that the rate of suicide in bipolar disorder is significantly elevated compared to the rate in the general population. One pooled analysis that examined 28 international studies in bipolar disorder found a one-year incidence rate of 0.40%, compared to the general international baseline rate of 0.0143%. Tondo L. *et al.* Suicidal Behaviour in Bipolar Disorder: Risk and Prevention. *CNS Drugs* 17:491-511 (2003). Bipolar disorder is relatively common and presents elevated risks of premature mortality, the most significant source being a very high risk of suicide. *Id.* at 492, 505. In fact, "[s]uicide rates, averaging 0.4% per year in men and women diagnosed with bipolar disorder, are > 20-fold higher than in the general population." *Id.* at 491.

Patients suffering from anxiety disorders are likewise at a significantly greater risk for suicide. A review of the FDA database of persons participating in anti-anxiety trials (n = 20,076) estimated the rate of suicide to be 0.193% per year. Khan A., *et al.* "Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database," *J of Affective Disorders* 68:183-190 (2002). This "suicide risk among patients with anxiety disorders is higher than in the general population by a factor of ten or more (CDC, 2000)." *Id.* at 189. "[P]atients with depressive disorders and psychotic disorders have a suicide risk 60-70 times higher than the general population." Khan *et al.* at 189.

Epidemiologic data also indicate that persons with chronic pain (chronic pain patients or CPPs) commit suicide or attempt suicide more frequently than the general population. A review was conducted of studies that examined the association between

chronic pain and suicide from 1966 to 1999. Fishbain, D.A. Association of chronic pain and suicide. *Seminars in Clinical Neuropsychiatry* 4:221-27 (1999). "Two studies [addressing suicide completion that were reviewed] found that the suicide rate for CPPs is two to three times greater than the general population." *Id.* at 224. "One controlled study indicated that subjects with low back pain had a significantly increased risk of completing suicide versus subjects without low back pain." *Id.* The studies on suicide ideation showed "a very high prevalence of suicidal ideation within CPPs ranging from 17% to 66%." *Id.*

Patients with epilepsy are also at an increased risk for suicide compared with the general population. Reported rates of suicide in the published literature for epilepsy provide a lifetime prevalence rate from less than 1% to 25%, with an average rate of 11.5%. Jones, J.E. et al., "Rates and risks for suicide, suicidal ideation, and suicide attempts in chronic epilepsy," *Epilepsy and Behavior* 2003; S31-38. This rate is significantly higher than the rate for the general population. *Id.* at S37. "Psychiatric comorbidity is a primary risk factor for suicide[,]" and "[i]ndividuals with epilepsy appear to have elevated rates of Axis I disorders ranging from 19 to 62% with rates of major depressive episodes ranging from 32 to 48%." *Id.* Individuals with epilepsy also have higher rates of suicide attempts compared with the general population. *Id.*

It is important to consider the background incidence rates of suicide in patients with epilepsy, psychiatric disorders, and chronic pain in analyzing the postmarket adverse event data for Neurontin. Despite the assertions of Plaintiffs' expert, Cheryl Blume, FDA epidemiologists and clinicians consider the background rates of suicidal behavior in these patient populations in making a clinical judgment as to the significance of the reports of suicidal behavior associated with the use of Neurontin. In assessing any potential association between Neurontin and suicidal behavior, it is especially important to be able to account for confounding factors, such as co-morbid conditions and concomitant medications. Such analyses are difficult, if not impossible, when using spontaneous adverse event data. Any conclusions based on spontaneous adverse event data must be limited to those that are "hypothesis generating" because of well-documented limitations of these data. Additionally, the complexity of analyzing spontaneous postmarketing adverse event in the face of high background rates of suicide highlights the importance of the need to analyze controlled clinical trial data in order to draw reliable conclusions as to the existence of an association between Neurontin and suicide.

Controlled clinical-trial data provides the most reliable scientific evidence for basing regulatory decisions regarding the association between Neurontin and suicide or suicidal behavior. In the April 12, 2005 letter in response to the Citizen's Petition, Dr. Katz noted that "in the absence of an appropriate control group, it will be difficult, if not impossible, to assess the role of any factors that might explain these events, such as

concomitant medications." Letter from Dr. Russell Katz, Director, FDA Division of Neuropharmacology, to Andrew Finkelstein at p. 1 (April 12, 2005). Dr. Katz then explained that a controlled-trial analysis is "crucial to deciding the obviously important question of whether or not these drugs do increase the risk of suicidality." *Id.* Consistent with this guidance, the FDA asked all AED manufacturers in March 2005 to undertake a comprehensive analysis of their controlled-trial data for "possibly suicide-related" adverse events. Letter from Dr. Russell Katz, Director, FDA Division of Neuropharmacology to Pfizer (March 16, 2005) Pfizer_LKnapp_0062278. As demonstrated in the record in this case, that FDA relies upon controlled clinical trial data when making important safety assessments that can impact the language of package inserts.

A. Analysis of Clinical-Trial Data

Per FDA's directive, in 2006, the AED suicidality analysis submitted by Pfizer employed a scientific methodology developed by expert psychiatrists at Columbia University. FDA Division of Neuropharmacology to Pfizer (March 16, 2005) Pfizer_LKnapp_0062278. This methodology, which had been used in other suicidality reviews such as the SSRI analysis, provided a classification system for suicide-related events. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. Am J Psychiatry 2007; 164:1035-1043. The events, once identified, were analyzed by psychiatrists blinded to treatment assignment and placed into one of the following six categories: completed suicide (code 1); suicide attempt (code 2); preparatory acts towards imminent suicidal behavior (code 3); self-injurious behavior, intent unknown (code 4); suicidal ideation (code 5); and not enough information (code 6). *Id.*

Pfizer submitted the results of its analysis of the Neurontin controlled-trial data to FDA in June of 2006. The results revealed that of the 5,194 patients who took Neurontin in the controlled trials, there were no cases of completed suicide or attempted suicide. Response to FDA Suicidality Request (June 22, 2006) at p. 4. Pfizer_MEvertsz_0079431. Similarly, there were no cases of "preparatory acts towards imminent suicide behavior." *Id.* The incidence of suicidal ideation was nearly identical to that of placebo patients, specifically 0.039% in Neurontin patients and 0.037% in placebo patients. *Id.* Only one of the 5,194 gabapentin-treated patients exhibited self-injurious behavior. *Id.* The results from the June 2006 submission are consistent with the findings of earlier analyses that Pfizer has undertaken at the FDA's request.

The controlled clinical trial data show no association between Neurontin and depression. The controlled-trial data from the epilepsy studies reveal that 1.8 percent of Neurontin patients reported treatment-emergent depression compared to 1.1 percent of

placebo patients. First Safety Update at Table 9. Dr. Blume has conceded that these differences are not statistically significant. Blume Depo at pp. 538-39; 540, 546. The controlled-trial data from the neuropathic pain trials also fails to show any association between Neurontin and depression; treatment-emergent depression was more common in patients on placebo than patients on Neurontin. Specifically 2.2% of patients on placebo reported treatment-emergent depression compared to 1.3 percent of patients on Neurontin. Dr. Hertz Review, Table 7.20. Similarly, more patients on placebo (0.7 percent) withdrew because of depression than patients on Neurontin (0.4 percent). PHN ISS at Table 24. In total, these data fail to establish a risk for suicide or suicidal behavior in patients treated with Neurontin as compared to patients treated with placebo.

Data from the three controlled clinical studies for psychiatric disorders (social phobia, bipolar disorder, and panic disorder) also fail to show any association with depression or suicidal behavior. For instance, in the bipolar disorder placebo-controlled study, there were two patients on placebo who reported suicidal ideation compared to zero patients on Neurontin. Research Report 720-04174 (March 26, 1999). Similarly, there were no suicide-related events or depression events reported by patients in the controlled studies on social phobia and panic disorder. Research Report 720-03850 (March 19, 1998); Research Report 720-03851 (April 9, 1999).

As reflected in Appendix B.3 of the epilepsy Third Safety Update, the clinical trial data do not show a dose response for Neurontin and depression. RR-Reg 720-03236, NDA 20-235, Appendix B.3 (May 12, 1993). Controlling for the length of exposure in the Neurontin-treated groups, patients reported depression at approximately the same frequency in the higher dosages as the lower dosages. The total duration of exposure was 1,322 weeks at the 300 mg dose, 5,284 weeks at the 600 mg dose, 7,626 weeks at the 900 mg dose, 34,949 weeks at the 1200 mg dose, 22,696 weeks at the 1800 mg dose, and 35,196 weeks at the 2400 mg dose. *Id.* Accordingly, the number of depression events in the higher doses is numerically greater than the lower doses because "patients at the higher dosages had greater opportunity to experience adverse events." RR-Reg 720-02957, Integrated Summary of Safety, NDA 20-235 at p. 72 (November 19, 1991). This does not reflect a dose-response relationship.

No scientific, medical, or regulatory body has ever concluded that Neurontin is associated with or causes suicidal behavior. FDA has never concluded that Neurontin causes suicide, and FDA has never suggested that a suicide-related warning or suicide-related precaution be included in the labeling The totality of the human experiential data fails to establish or support an association between Neurontin and suicide or suicidal behavior.

B. EMEA Analysis

In December 2005, Pfizer submitted an updated postmarketing report to the European Medicines Agency ("EMEA") and its advisory committee, the Committee for Medicinal Products for Human Use ("CHMP"). Pfizer, Inc., Response to EMEA (December 14, 2005) Pfizer_MEvertsz_0084480. The cutoff date for the postmarketing report submitted to the EMEA was July 31, 2005. Pfizer, Inc., Response to EMEA, Appendix 4 (December 14, 2005) Pfizer_JMohan_0000479 ("Mohan Report"). Whereas the September 2004 postmarketing report revealed 35 reports of suicide and 73 reports of suicide attempt, the report submitted in December 2005 identified 111 reports of completed suicide and 192 reports of attempted suicide with an estimated exposed population of 14 million patients. A month after receiving this report, the EMEA issued a report concluding that "the available data show no clear evidence for a causal association between gabapentin and suicide or suicide attempt and show no causal association for a risk of psychotic or mood disorders in patients with a positive history of psychotic illness." EMEA, Joint Response Assessment Report at 28 (January 12, 2006) Pfizer_MPatel_0252359. No regulatory agency in the world has issued a finding contradicting the EMEA's conclusions.

VIII. Conclusions

It is my opinion that Pfizer and its predecessor Warner-Lambert/Parke-Davis appropriately developed, investigated, and labeled Neurontin. It is my opinion that the Neurontin package insert appropriately summarized and disclosed safety and effectiveness information to the prescribing public. It is my opinion that physicians and other prescribers were provided with the essential information needed to safely and effectively prescribe Neurontin, including appropriate information concerning reports of suicide, suicidal behavior and depression arising from the clinical trials populations and from patients receiving Neurontin following market approval. It is my opinion that the package insert fully complied with FDA regulations in terms of the information required and the information provided.

It is my opinion that the Neurontin NDA and supplements for the epilepsy and postherpetic neuralgia indications, including the Safety Updates, appropriately identified, summarized, and reported adverse events involving suicidal behavior, depression, and other psychiatric-related reports.

Since December 30, 1993, when Neurontin was initially approved, FDA has not sought or required warnings, precautions or contraindications addressing a risk of suicide, suicidal behavior or other psychiatric adverse events be added to the label, even though such additions have been proposed or by third parties involved with civil litigation. FDA has not required a label prohibiting or advising against off-label uses, as permitted under 21 C.F.R. § 201.57(c)(2)(ii)(2006). Furthermore, language describing Neurontin's mechanism of action had been including draft labels submitted by Pfizer and that language was specifically removed from the label by FDA on two separate occasions. In my clinical experience, this type of information serves no useful purpose

in informing physicians or other prescribers considering the use of Neurontin for their patients. I agree with Dr. McCormick's statements in her affidavit regarding FDA's rational for deleting Pfizer's proposed language concerning Neurontin's mechanism of action from the package insert. I also agree with Dr. McCormick's assessment that the Neurontin label appropriately and accurately identifies the risk benefit profile of Neurontin and that the addition of language regarding monoamines and gabapentin would have little importance to a prescribing clinician.

It is also my opinion that the data from the Neurontin controlled clinical trials do not demonstrate evidence of an increased risk for suicide, suicidal behavior or depression among persons exposed to Neurontin, much less a causal association between the use of Neurontin and suicide, suicidal behavior or depression. The controlled clinical trial data as well as epidemiologic data demonstrating increased risks for these outcomes in the patient populations for whom Neurontin is prescribed overwhelms the highly anecdotal quality of evidence to the contrary based on case listings and calculations of percentages of adverse events offered by plaintiff's expert.

It is my opinion that Neurontin has always been appropriately labeled and that the development of the product and its label has fully complied with FDA regulatory requirements throughout its development and marketing history. It is my opinion that since initial approval in December 1993, the Neurontin package insert has adequately and appropriately advised prescribing physicians and other health care providers in the US of the potential risks and benefits associated with the use of Neurontin.

December 20, 2007

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